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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KLARQUIST SPARKMAN CAMPBELL
LEIGH & WHINSTON, LLP
One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, OR 97204

EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,570	CROTEAU ET AL.	
	Examiner	Art Unit	
	Kathleen M Kerr	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8-11,14,16,18 and 23-27* is/are pending in the application.

4a) Of the above claim(s) *1,9,18 and 23-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8,10,11 and 14* is/are rejected.

7)☒ Claim(s) *3-6 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 11, mailed on September 23, 2002), Applicants filed an election received on October 29, 2002 (Paper No. 12). Claims 1, 3-6, 8-11, 14, 16, 18, and 23-27 are pending in the instant Office action.

Election

2. Applicants' election of SuperGroup B, Claims 3-6, 8, 10, 11, 14, 16, and 24-27 as they related to TAX6 (SEQ ID NOs:44/45), in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (M.P.E.P. § 818.03(a)).

Applicants incorrectly cited "Group XV" as SuperGroup B relating to SEQ ID NO:44; the correct Group is Group XXXV relating to SEQ ID NOs:44/45. This is the Group that will be examined herein since Applicants clearly state their intention to elect nucleic acid claims related to SEQ ID NO:44 (TAX6).

Claims 1, 9, 18, and 23-27 are withdrawn from further consideration as non-elected inventions. Claims 3-6, 8, 10, 11, 14, and 16 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the U.S. non-Provisional Application No. 09/457,046 (DIV) filed on December 7, 1999 and

09/411,145 (CIP) filed on September 30, 1999 as requested in the declaration and the first lines of the specification. The Examiner notes that the elected Group drawn to TAX6 does not have priority back to the earliest date of September 30, 1999 since 09/411,145 teaches only TAX1 and TAX2.

Information Disclosure Statement

4. The information disclosure statement filed on September 4, 2001 (Paper No. 5) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

Compliance with the Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) In Figure 4, peptide and DNA sequences are disclosed. The SEQ ID NOs listed in the figure do not clearly define whether they relate to the peptide or DNA sequences, and some of these sequences do not have SEQ ID NOs.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of

the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Objections to the Specification

6. The specification is objected to for being confusing with respect to the sequence listing. The sequence listing contains 74 sequences. Every SEQ ID NO is mentioned in the specification and/or the claims except SEQ ID NOs: 61-74. It is unclear why said sequences are in the sequence listing if they are not described in the specification. All SEQ ID NOs in the sequence listing must be described in the specification. Appropriate correction is required.

7. The specification is objected to for updated lacking continuity data in the first paragraph. In the first paragraph, U.S. non-Provisional Application No. 09/457,046 must be noted as now patented and U.S. non-Provisional Application No. 09/411,145 must be noted as now abandoned. Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

8. The specification is objected to because the title is not descriptive. A new title is required that is clearly indicative of the invention to which the elected claims are drawn (see M.P.E.P. § 606.01). The Examiner suggests the following new title:

---Nucleic Acid Molecules Encoding 10-Deacetylbaccatin III-10-O-Acetyl Transferase and Related Products---

9. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)). It is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of the full name of the enzymes disclosed in the specification and the source species, *Taxus cuspidata*, for completeness.

10. The specification is objected to for inappropriate notation of an internet address. On page 15, line 14 and line 16, internet addresses are cited in an unacceptable form. See M.P.E.P. § 707.05(e) for the acceptable notation of an internet address.

11. The specification is objected to for having confusing characters throughout the specification. It seems that some symbols (Greek lettering) were transposed to other characters. See page 29, line 22 where a backwards "E" should be the symbol for beta ---β--- and on page 32, line 15 where an upside-down "A" should be the symbol for alpha ---α---. Numerous examples are throughout the specification; Applicants must correct them all.

12. The specification is confusing in its varied use of the enzyme name for the claimed nucleic acid molecule encoding the TAX6 enzyme.

a) On page 7, the term "acyltransacylase" is used to describe TAX6.
b) On page 10, the term "O-acetyl transferase" is used.
c) On page 15, the terms "acyltransferase" and "transacylase" are noted as interchangeable; there is no mention of acetyl transferases in this paragraph.
d) On page 21, the term "O-acetyl transferase" is used.
e) On page 33, the term "transacylase" is used.
f) On page 35, the term "O-acetyl transferase" is used.

The Examiner understands acyltransferases to transfer and more generic, acyl group while acetyltransferase to specifically transfer an acetyl group. Clarification of the enzyme name and category is required.

Claim Objections

13. Claims 3-6 are objected to for depending from a non-elected claim, Claim 1.

14. Claim 16 is objected to for depending from a cancelled claim, Claim 15. Claim 16 cannot be further treated on its merits.

15. Claims 3-6, 8, 10, 11, and 14 are objected to for containing non-elected subject matter. References to all but SEQ ID NOs: 44 and 45 are non-elected and must be removed from the claims.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

16. Claims 8, 10, 11, 14, and 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The activity of a transacylase is unclear when used with respect to TAX6 that seems to be defined as an acetyltransferase. Clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 8, 10, and 11 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 8 is drawn to nucleic acid molecules that hybridize to fragments of SEQ ID NO:44 and that have transacylase activity. The hybridizing language (considered to be about 50% identical and using the conditions defined on page 41), by virtue of the fragment language, does not impart a definite structure for the claimed nucleic acid molecules; the functional language does not impart a clear function (see rejection under 35 U.S.C. § 112, second paragraph above).

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of

the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification discloses a nucleic acid molecule encoding 10-deacetylbaccatin III-10-O-acetyl transferase from *Taxus cuspidata*, SEQ ID NO:44. Applicants have fully described the genus relating to said SEQ ID NO with both definite sequence limitations and clear functional limitations (i.e., having 10-deacetylbaccatin III-10-O-acetyl transferase activity). However, the genus of the instant claims also contains polynucleotides of any sequence and having a vague function. Applicants have not fully described said genus.

The Examiner suggests, in Claim 8, the removal of the phrase "fragments thereof" and the insertion of clear functional language to obviate the instant rejection.

18. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 14 is drawn to nucleic acid molecules having at least 60% identity with SEQ ID NO: 44, but citing no clear function (see rejection under 35 U.S.C. § 112, second paragraph above).

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University

of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant specification discloses polynucleotides with at least 60% identity with SEQ ID NO:44. Applicants have fully described the genus relating to said SEQ ID NO with both sequence identity limitations and functional limitations (i.e., having 10-deacetylbaccatin III-10-O-acetyl transferase function). However, the genus of the instant claims also contains polynucleotides within the sequence identity limitations, but having different function. Applicants have not fully described a genus that has sequence identity limitations in the absence of functional limitations.

The Examiner suggests, in Claim 14, the insertion of clear functional language to obviate the instant rejection.

19. Claims 8, 10, 11, and 14 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for nucleic acid molecules having 90% sequence identity (or hybridizing under very high stringency conditions) with SEQ ID NO:44, does not reasonably provide enablement for nucleic

acid molecules having 60% sequence identity (or hybridizing under low stringency conditions) with SEQ ID NO:44. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The amount of experimentation required of one of skill in the art to use the claimed invention to the full extent of its scope is undue.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

Applicants present no guidance or working examples of the use of polynucleotides that have such low sequence identity with respect to SEQ ID NO:44. The nature of the invention is such that the DNA encodes a functional protein, a 10-deacetylbaccatin III-10-O-acetyl transferase useful in the biosynthetic pathway of Taxol; and with such a great deviation from the known sequence, the predictability of functionality becomes extremely low. Such enormous breadth and unpredictability renders the instant claims not enabled to the full extent of their scope without undue experimentation.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

20. Claim 8 is rejected under 35 U.S.C. § 102(b) as being anticipated by GenBank Accession Number X66785 (see IDS). The instant claim is drawn to a nucleic acid molecule that hybridizes under low-stringency conditions to a probe comprising a fragment of SEQ ID NO:44 wherein said nucleic acid molecule encodes a protein having transacylase activity.

GenBank Accession Number X66785 teaches a 3535 bp mRNA sequence that encodes a transacylase, particularly dihydrolipoyl transacylase (E2). The sequence

limitations require no definite structure since all probes comprise "a fragment" of SEQ ID NO:44, a fragment being as small as a single nucleotide.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 8, 10, 11, and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Menhard *et al.* (see IDS) or Zocher *et al.* (see IDS), either in view of GenBank Accession Number AF456342, Matsudaira, Wozney, and Sambrook *et al.* The instant claims are drawn to nucleic acid molecules at least 60% identical to SEQ ID NO:44 and encoding an acyltransferase.

Menhard *et al.* teach a purified protein from *Taxus chinensis* that performs an acetyltransferase reaction on 10-desacetylbaccatin III (see Abstract).

Zocher *et al.* teach an isolated protein from *Taxus baccata* that acetylates 10-deacetylbaccatin-III (see Abstract).

Neither Menhard *et al.* nor Zocher *et al.* teach the protein sequence or encoding DNA sequence of their acetyltransferases from *T. chinensis* and *T. baccata*, respectively. The natural relatedness of sequence from *Taxus* species of *cuspidata*, *chinensis* and *baccata* is very high as seen in the attached alignment of the *cuspidata* (SEQ ID NO:44) and *baccata* (GenBank Accession Number AF456342) sequences (the *baccata* sequence

was made available after the priority date of the instant claims and cannot be used as anticipatory art, but is used herein as post-filing date evidence allowed by M.P.E.P. § 2131.01). Moreover, the reactions catalyzes by the isolated proteins of Menhard *et al.* and Zocher *et al.* are identical to the reaction described for TAX6 in the instant application.

The skill of an artisan in the field of molecular biology at the time the invention was made was such that the artisan could use conventional techniques to: 1) obtain a partial amino acid sequence of an isolated polypeptide; 2) synthesize a degenerate polynucleotide probe based on the partial amino acid sequence; 3) use the polynucleotide probe to screen a cDNA or genomic library and identify a full length cDNA or genomic clone; 4) construct expression vectors comprising the isolated cDNA or genomic clone; and 5) transform a host cell with an expression vector comprising the isolated cDNA or genomic clone. Specifically, Matsudaira teaches methods for the determination of N-terminal amino acid sequences (see pages 602-604), and Wozney teaches methods of using purified proteins to clone the corresponding genes (see page 738). Wozney teaches the considerations for the selection of peptide candidates for the production of degenerate oligonucleotide probes, synthesis of oligonucleotide probes, screening of genomic or cDNA libraries, and isolation and amplification of cDNA or genomic clones. (see pages 738-751). The teachings of the Matsudaira and Wozney teach methods that enable the skilled artisan at the time the invention was made to produce the DNA fragments that encode the isolated acetyltransferases as taught by either Menhard *et al.* or Zocher *et al.* Thus, the teachings of the isolated or purified acetyltransferases by either Menhard *et al.* or Zocher *et al.* render the DNA fragments encoding said acetyltransferases obvious,

because the prior art teachings suggest all the elements of said DNA fragments, and the prior art teachings enabled the artisan to produce said DNA fragments claimed.

Sambrook *et al.* teach vectors, promoters and DNA sequences required for the transcription of cloned copies of genes, generally, and the translation of their mRNAs in *Escherichia coli* (see pages 404-411) and eukaryotic cells (see pages 412-433). Sambrook *et al.* also teach methods of maximizing the expression of cloned genes in transformed host cells (see page 431). The teachings of the Sambrook *et al.*, in light of the above teachings of Matsudaira and Wozney, teach methods that enable the skilled artisan at the time the invention was made to produce acetyltransferase-encoding DNA fragments from *Taxus* species in plasmids for recombinant expression of acetyltransferases. Thus, the teaching of the isolated acetyltransferase by either Menhard *et al.* or Zocher *et al.* renders the DNA fragments encoding acetyltransferases and their use in the recombinant expression of acetyltransferases obvious, because the prior art teachings suggest all the elements of the DNA fragments and their use, and the prior art teachings enabled the artisan to produce the DNA fragments and recombinantly express them.

At the time the invention, one of ordinary skill in the art would have been motivated to combine the teachings of Menhard *et al.* or Zocher *et al.* with supporting references Matsudaira, Wozney, Sambrook *et al.* to formulate methods of recombinant expression of the characterized acetyltransferase for the purpose of producing large quantities of the acetyltransferase for further study. One would have been motivated to such studies because of the crucial role this acetyltransfase plays in the biosynthesis of Taxol, a potent and successful anticancer drug (see Menhard *et al.*).

Other Art of Interest

22. The following reference is cited to complete the record:

a) Walker *et al.* Molecular cloning of a 10-deacetylbaccatin III-10-O-acetyl transferase cDNA from Taxus and functional expression in *Escherichia* coli. PNAS. January, 2000. 97(2):583-587.

Conclusion

23. Claims 3-6 and 16 are objected to; Claims 8, 10, 11, and 14 are rejected for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
January 20, 2003